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Ethnic variability in methotrexate pharmacogenetics among rheumatoid arthritis populations: a narrative review

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ABSTRACT

Methotrexate is the recommended first-line conventional disease-modifying antirheumatic drug for rheumatoid arthritis; interindividual variability in treatment response and toxicity remains a major clinical challenge. Pharmacogenomics provides a biological basis for this variability, yet reported associations between genetic polymorphisms and methotrexate outcomes are often inconsistent across populations. This narrative review synthesizes current evidence on ethnic variability in methotrexate pharmacogenetic associations among patients with rheumatoid arthritis. A structured literature search was conducted in PubMed/MEDLINE, Scopus, and Google Scholar up to January 2026, including human studies evaluating genetic polymorphisms in methotrexate-related pathways and reporting outcomes related to treatment effectiveness or toxicity. The available evidence is dominated by observational studies in populations of European and East Asian ancestry, with limited data from Southeast Asian cohorts. Polymorphisms in genes involved in methotrexate transport, intracellular activation, folate-dependent metabolism, and drug efflux demonstrate substantial interethnic differences in allele frequencies and reported clinical associations. Variants in folate metabolism genes are more consistently associated with methotrexate-related toxicity than with treatment effectiveness, whereas transporter and downstream pathway variants show population-dependent and heterogeneous associations with effectiveness. These inconsistencies are further influenced by methodological heterogeneity, including differences in outcome definitions, methotrexate dosing, folate supplementation, sample size, and adjustment for concomitant therapies. Overall, ethnic variability appears to be a key determinant of methotrexate pharmacogenetic associations in rheumatoid arthritis. Population-specific studies using standardized disease activity outcomes are required, particularly in underrepresented Southeast Asian populations especially Indonesia, to support equitable implementation of precision medicine strategies.

ABSTRACT

Metotreksat merupakan obat lini pertama yang direkomendasikan untuk artritis reumatoid, namun variasi respons klinis dan kejadian toksisitas antar pasien masih menjadi tantangan utama dalam praktik klinik. Farmakogenetik memberikan dasar biologis terhadap variasi tersebut, tetapi hubungan antara polimorfisme genetik dan luaran terapi metotreksat sering dilaporkan tidak konsisten antar populasi. Tinjauan naratif ini bertujuan merangkum bukti terkini mengenai variasi etnis pada asosiasi farmakogenetik metotreksat pada pasien artritis reumatoid. Pencarian literatur terstruktur dilakukan pada PubMed/MEDLINE, Scopus, dan Google Scholar hingga Januari 2026, mencakup studi pada manusia yang mengevaluasi polimorfisme genetik pada jalur farmakologi metotreksat serta melaporkan luaran efektivitas atau toksisitas terapi. Bukti yang tersedia didominasi oleh studi observasional pada populasi leluhur Eropa dan Asia Timur, sementara data dari populasi Asia Tenggara masih terbatas. Polimorfisme pada gen yang berperan dalam transport metotreksat, aktivasi intrasel, metabolisme bergantung folat, dan pengeluaran obat menunjukkan perbedaan frekuensi alel dan asosiasi klinis antar etnis. Varian pada gen metabolisme folat lebih konsisten berhubungan dengan toksisitas dibandingkan efektivitas terapi, sedangkan varian transporter dan jalur hilir menunjukkan asosiasi yang bergantung pada populasi dan heterogen. Variasi metodologis, termasuk perbedaan definisi luaran, dosis metotreksat, suplementasi folat, ukuran sampel, dan pengendalian terapi penyerta, turut memperkuat ketidakkonsistenan temuan. Secara keseluruhan, variasi etnis diduga menjadi determinan penting dalam farmakogenetik metotreksat pada artritis reumatoid, sehingga diperlukan penelitian spesifik populasi dengan luaran aktivitas penyakit yang terstandarisasi, khususnya pada populasi Asia Tenggara terkhususnya Indonesia.

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INTRODUCTION

Precision medicine has emerged as a central paradigm in the management of autoimmune diseases, with pharmacogenomics playing an essential role in explaining interindividual variability in drug response. Pharmacogenomics examines how genetic variation influences drug pharmacokinetics and pharmacodynamics, thereby affecting therapeutic efficacy and safety.[1] In rheumatoid arthritis (RA), where treatment response is influenced by complex inflammatory and immunological pathways, genetic determinants may substantially contribute to therapeutic variability and clinical outcomes.[2,3]

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterised by persistent synovial inflammation, progressive joint destruction, and substantial functional impairment.[4,5] The global prevalence of RA has continued to rise, with an estimated 17.6 million affected individuals worldwide in 2020, and projections indicating further increases over the coming decades.[6] Disease activity is commonly evaluated using a validated composite instrument such as the Disease Activity Score-28 (DAS-28), which integrates clinical and laboratory parameters including swollen joints, tender joints, acute phase response, and overall health to provide a continuous assessment of rheumatoid arthritis disease activity to guide therapeutic decision-making.[7]

Methotrexate (MTX) is the first-line conventional synthetic disease-modifying antirheumatic drug (csDMARD) for RA due to its established efficacy, flexible dosing, and favourable cost-effectiveness profile.[5] Despite its widespread use, considerable variability exists in treatment response and toxicity.[8] Methotrexate is particularly sensitive to genetic variability because its therapeutic activity depends on active cellular transport and intracellular polyglutamation processes. MTX requires transporter-mediated uptake and intracellular conversion into methotrexate polyglutamates to exert its anti-inflammatory effects. Consequently, polymorphisms in genes involved in methotrexate transport, folate metabolism, intracellular polyglutamation, and drug efflux pathways may substantially influence intracellular drug exposure, treatment response, and toxicity risk.[3,9]

A key factor contributing to these discrepancies is ethnic variability in genetic architecture. Ethnicity, often used as a surrogate for shared genetic ancestry, may influence the distribution of pharmacogenetically relevant variants, reflecting population-specific allele frequency distributions, haplotype structures, and linkage disequilibrium patterns.[10,11] Polymorphisms in methotrexate-related genes, including Solute Carrier Family 19 Member 1 (*SLC19A1*), Methylenetetrahydrofolate Reductase (*MTHFR)*, ATP-Binding Cassette Subfamily G Member 2 (*ABCG2*), and 5-Aminoimidazole-4-Carboxamide Ribonucleotide Transformylase (*ATIC*) exhibit marked differences in allele frequencies across Caucasian, East Asian, South Asian, and other populations. These genes play important roles in the pharmacokinetic and pharmacodynamic pathways of methotrexate. Ethnic variability in these polymorphisms may therefore influence transporter activity, intracellular methotrexate exposure, treatment efficacy, and toxicity profiles among rheumatoid arthritis patients. Recent pharmacogenetic studies and reviews further support the clinical relevance of these genes in personalized methotrexate therapy and precision medicine approaches in rheumatoid arthritis management.[12-15]

Failure to account for ethnic variability and population structure may lead to inconsistent pharmacogenetic findings across studies. Differences in allele frequencies and genetic

backgrounds between populations can influence the effects of methotrexate-related genetic variants on treatment response and toxicity. In addition, methodological differences, such as variations in outcome definitions, methotrexate dosing regimens, folate supplementation, sample sizes, and analytical methods, may further contribute to conflicting results. These multifactor may limit the consistency, interpretation, and applicability of existing methotrexate pharmacogenetic evidence in rheumatoid arthritis populations.[10,15]

Several pharmacogenetic markers have been increasingly investigated in rheumatoid arthritis to better predict methotrexate efficacy and toxicity. Variants in genes involved in methotrexate transport, folate metabolism, intracellular polyglutamation, and drug efflux pathways, including *SLC19A1*, *MTHFR*, *FPGS*, *GGH*, and ATP-Binding Cassette (ABC) transporters, have been associated with interindividual variability in treatment response and adverse drug reactions. Recent advances in pharmacogenomics have further emphasized the potential role of population-specific genetic profiling in supporting personalized methotrexate therapy and improving therapeutic outcomes among patients with rheumatoid arthritis.[18-20]

Along with these considerations, a comprehensive narrative synthesis of methotrexate pharmacogenetics that explicitly addresses ethnic variability is warranted. This review aims to integrate population-level allele frequency data, pharmacogenetic association studies, and methodological sources of heterogeneity to provide a coherent framework for understanding interethnic differences in methotrexate response among rheumatoid arthritis populations. By highlighting gaps in current evidences and methodological limitations, this review seeks to inform future research directions and support the advancement of precision medicine in rheumatoid arthritis management.

METHODS

This study was conducted as a narrative review employing a pathway-based synthesis approach, aimed to provide an interpretative synthesis of published evidence focusing on ethnic variability in methotrexate pharmacogenetics among patients with rheumatoid arthritis. A structured literature search was conducted to identify relevant studies examining ethnic variability in methotrexate pharmacogenetics among patients with rheumatoid arthritis. Electronic databases including PubMed/MEDLINE, Scopus, and Google Scholar were searched for eligible studies published between 2000 and January 2026. Search terms were combined using Boolean operators AND and OR, including “methotrexate” AND “rheumatoid arthritis” AND (“pharmacogenetics” OR “genetic polymorphism”) AND (“ethnic differences” OR ethnicity OR ancestry) AND (“SLC19A1” OR “RFC1” OR “MTHFR” OR “FPGS” OR “ATIC” OR “ABC transporters”). Additional population-related terms such as “Asian ancestry” were applied to capture region-specific evidence. Additional population-related terms such as “Asian ancestry” were also incorporated to capture region-specific evidence. Detailed search strategies for each database are presented in TABLE 1.

TABLE 1. Literature Search Strategies Across Electronic Databases

Database	Search Strategy
PubMed/MEDLINE	("methotrexate" AND "rheumatoid arthritis") AND ("pharmacogenetics" OR "genetic polymorphism") AND ("ethnic differences" OR ethnicity OR ancestry)
Scopus	TITLE-ABS-KEY ("methotrexate" AND "rheumatoid arthritis" AND pharmacogenetics)
Google Scholar	"methotrexate pharmacogenetics rheumatoid arthritis ethnicity SLC19A1 MTHFR"

Inclusion criteria were human studies involving RA patients receiving MTX therapy, evaluation of MTX-related genetic polymorphisms, and reporting of clinical outcomes related to effectiveness or toxicity. Animal studies, in vitro studies, and studies not related to MTX pharmacogenetics were excluded. Reference lists of relevant articles were also screened to identify additional studies. Identified studies were synthesized using a pathway-oriented framework, grouping findings according to methotrexate transport, intracellular metabolism, folate-dependent pathways, and drug efflux mechanisms. Within each pathway, evidence was further compared across ethnic populations to highlight interethnic variability, differences in allele frequency distribution, and sources of methodological heterogeneity.

RESULTS

The literature search identified studies primarily consisting of observational pharmacogenetic investigations evaluating methotrexate-related genetic polymorphisms and clinical outcomes in rheumatoid arthritis populations. After screening and eligibility assessment, the included studies mainly investigated polymorphisms involved in methotrexate transport, intracellular polyglutamation, folate-dependent metabolism, and drug efflux pathways. The reviewed evidence was predominantly derived from Caucasian and East Asian populations, whereas comparatively limited data were available from Southeast Asian and Middle Eastern cohorts. Key genes frequently evaluated across studies included *SLC19A1 (RFC1)*, *MTHFR*, *Folylpolyglutamate Synthase (FPGS)*, *Gamma-Glutamyl Hydrolase (GGH)*, *5-Aminoimidazole-4-Carboxamide Ribonucleotide Transformylase (ATIC), and ATP-Binding Cassette (ABC) transporters such as ATP-Binding Cassette Subfamily B Member 1 (ABCB1), ATP-Binding Cassette Subfamily C Member 2 (ABCC2), and ATP-Binding Cassette Subfamily G Member 2 (ABCG2).*

Across studies, genetic variants were primarily evaluated within key methotrexate (MTX) pharmacological pathways, including cellular transport, intracellular polyglutamation, folate-dependent metabolism, and drug efflux. However, substantial heterogeneity was evident in study design, sample size, MTX dosing regimens, folate supplementation practices, and clinical outcome definitions. Consequently, the comparability and generalisability of pharmacogenetic findings between Caucasian, Asian, and Middle Eastern populations remain limited. These studies have primarily examined polymorphisms involved in methotrexate transport, intracellular metabolism, folate-dependent pathways, and drug efflux, using diverse clinical endpoints related to treatment response and toxicity.[15,21]

Methotrexate Transport Pathway

Genetic polymorphisms affecting

methotrexate cellular transport have been among the most extensively investigated pharmacogenetic determinants of treatment response. In particular, SLC19A1/RFC1 (Solute Carrier Family 19 Member 1 / Reduced Folate Carrier 1), which encodes the reduced folate carrier responsible for methotrexate uptake into cells, has been repeatedly examined across ethnic populations.[22,23] In Caucasian populations, the rs1051266 (G80A) variant has been associated with a protective effect against methotrexate discontinuation due to adverse events in a univariate analysis involving 333 individuals of Caucasian ancestry.[24] However, other studies have reported inconsistent associations between this variant and methotrexate treatment response.[25,26] In Egyptian cohorts, the variant was associated with increased susceptibility to methotrexate treatment response.[23] Evidence from Asian ancestry has been more heterogeneous, with several studies reporting positive correlation[27-29] while others remained conflicted between efficacy and toxicity profiles[22] findings of its polymorphism. In contrast, studies conducted in Indonesian populations remain limited. Notably, rs1051266 (SLC19A1) was excluded in one large replication study due to a low genotype call rate, suggesting technical limitations in genotyping rather than absence of the variant in European populations. This methodological issue may partly explain the inconsistent associations reported for this single nucleotide polymorphism (SNP) across studies.[30] Collectively, findings across populations indicate an ethnicity-dependent pattern of association for SLC19A1.

Intracellular Methotrexate Metabolism

Genes involved in intracellular methotrexate metabolism have been less frequently evaluated and demonstrate greater inconsistency across studies. FPGS (Folylpolyglutamate Synthase), which catalyzes methotrexate polyglutamation and enhances intracellular drug retention, has shown variable associations with treatment response and toxicity in FPGS variants in Caucasian-Spain study is associated with treatment response and persistence, with concomitant associations with toxicity.[8]

Evidence from Asian cohorts is limited, research conducted with Japanese patients indicate that FPGS profile in the patient are different significantly from Caucasian population also a major determinant of intracellular conversion of MTX to MTXPG3-5. FPGS catalyzes the sequential addition of glutamate residues to methotrexate, resulting in the formation of methotrexate polyglutamates (MTXPGs), including MTXPG3–5, which are retained intracellularly and contribute to prolonged pharmacological activity. Variations in *FPGS* may therefore affect intracellular methotrexate accumulation, treatment persistence, therapeutic response, and toxicity profiles. Studies involving South Indian Tamil rheumatoid arthritis patients have reported associations between FPGS variants and methotrexate-related adverse events.[31] FPGS variants affect intracellular polyglutamation and treatment persistence hence correlated with 330 South Indian Tamil patients with RA were associated with MTX adverse events[32] while in other research it is associated with MTX therapy response[8] hence the clarity of diverse outcome in ethnicity is remain clear.

Similarly, genetic variation in GGH (Gamma-Glutamyl Hydrolase), the enzyme responsible for methotrexate deglutamation, has been associated with inconsistent clinical outcomes. Studies in Caucasian-Spain populations have reported heterogeneous findings,[8] while in the UK-based ancestor GGH are found to be associated (trend $p \leq 0.05$) with MTX efficacy.[33] Asian based studies find that GGH does not affect the effectiveness of methotrexate therapy.[15,32,33]

Folate-Dependent Pathways

Polymorphisms in genes regulating folate metabolism have been primarily examined in relation to methotrexate-related toxicity rather than treatment efficacy. Variants in MTHFR (Methylenetetrahydrofolate Reductase), particularly C677T and A1298C, polymorphisms and were observed in Chinese ancestry patients, these variants did not demonstrate reliable predictive value for clinical methotrexate response treatment outcomes.[34] While in rs17421511, and rs1476413 are having Positive response to MTX treatment (GG) in active flaring while rs4846051 MTHFR Increased the risk of MTX toxicity in 100 European descendant RA patients.[35] While in Tunisian descendant study, the involvement of the MTHFR C677T polymorphism is correlated to MTX toxicity.[36]

In contrast, polymorphisms in ATIC (5-Aminoimidazole-4-Carboxamide Ribonucleotide Transformylase) a key enzyme involved in purine synthesis inhibition and adenosine-mediated anti-inflammatory effects, have been evaluated in a smaller number of studies. Folate-dependent pathways were distinguished from core folate metabolism and included purine and pyrimidine synthesis pathways requiring folate-derived cofactors. Latest study in 647 Malaysian ethnicity population evaluate that polymorphism in ATIC C347G (rs2372536) and ATIC T675C (rs4673993), have a significant effect on the efficacy of MTX in RA patients.[15] Caucasian ancestry based research also finds the efficacy of the research.[33,37] While in Chinese population patients this polymoprhism remains unassociated with the outcomes of MTX therapy.[38] Evidence from various ethnic varieties remains conflicted, therefore with its limited previous studies. Further studies with Indonesian ancestry studies are needed.

Drug Efflux Transporters

Genetic variation in ABC (ATP-Binding Cassette) transporters, including ABCC2 (ATP-Binding Cassette Subfamily C Member 2) and ABCG2 (ATP-Binding Cassette Subfamily G Member 2), which mediate methotrexate efflux. Variants in these genes were most frequently associated with differences in methotrexate toxicity and, to a lesser extent, drug disposition, while associations with treatment efficacy were less consistently reported across studies. Pharmacogenetic analyses have demonstrated that genetic variation in ABCB1 (ATP-Binding Cassette Subfamily B Member 1), particularly rs1045642, is associated with variability in clinical response to methotrexate (MTX) among patients with rheumatoid arthritis. Ethnic-specific differences have been consistently reported. In East Asian populations, including Han Chinese,[20] and Japanese cohorts,[28] ABCB1 polymorphisms have been predominantly associated with increased MTX-related toxicity, notably MTX-induced elevations in hepatic enzyme levels. In contrast, studies conducted in Turkish populations have shown that the heterozygous ABCB1 C/T genotype is associated with non-response to MTX therapy. Furthermore, evidence from multi-country meta-analyses suggests that ABCB1 variants may contribute to higher rates of MTX drug resistance, underscoring substantial heterogeneity in pharmacogenetic effects across populations.

In populations of European ancestry, ABCB1 polymorphisms have also been linked to MTX toxicity, with studies in adult RA cohorts followed for approximately three months reporting associations between transporter gene variants and adverse treatment outcomes. MTX efflux is mediated primarily by members of the ATP-binding cassette (ABC) transporter family, including ABCB1, ABCC1–4, and

ABCG2, highlighting the central role of drug efflux mechanisms in determining intracellular MTX exposure.

Beyond ABCB1, polymorphisms in ABCC2, particularly rs3740066, rs4148396, and rs717620, have been significantly associated with European Alliance of Associations for Rheumatology (EULAR) good or moderate response, while rs3740066 and rs717620 were also associated with achieving low disease activity (LDA) based on DAS28-ESR. In addition, variants in ABCB1 (rs1128503, rs4148737) and ABCC3 (rs2277624, rs4148416) were significantly associated with changes in DAS28-ESR, indicating improved clinical efficacy. Consistent with these findings, ABCC2 polymorphisms have been proposed as potential predictors of clinical response to MTX in Chinese RA patients.[39]

Studies on pharmacogenetic risk factors for MTX toxicity and efficacy have produced conflicting data, potentially due to limited sample size, ancestry heterogeneity, and lack of accounting for comorbidities and other confounding factors.

Summary of Ethnic-Specific Pharmacogenetic Patterns

Overall, existing evidence highlights substantial ethnic variability in methotrexate pharmacogenetic associations involving drug transport, intracellular metabolism, folate-dependent pathways, and efflux mechanisms. Although the underlying pharmacological pathways support the biological plausibility of these associations, ethnic variability may substantially influence their clinical significance and consistency across populations.

While data from Caucasian and Asian populations provide a foundation for understanding pharmacogenetic variability, evidence from Southeast Asian populations remains limited and fragmented. A comparative synthesis of pharmacogenetic findings across interethnic groups is presented in TABLE 2.

While numerous studies have investigated the association between genetic polymorphisms and methotrexate response or toxicity in rheumatoid arthritis, the reported findings remain highly heterogeneous and, in some cases, contradictory. Several pharmacogenetic studies have demonstrated substantial methodological heterogeneity, particularly in outcome definition, population structure, and methotrexate exposure, which contributes to inconsistent findings across ethnic groups[15,25,33,43] Moreover, limited adjustment for important clinical confounders, such as corticosteroid use and concomitant conventional synthetic DMARDs, as an additional risk of biased associations. To contextualise the heterogeneity of reported associations, methodological limitations across key domains are summarised in TABLE 3. Addressing these limitations through standardized outcome measures, population-specific study designs, and robust analytical frameworks will be essential for advancing the clinical utility of pharmacogenetic markers in rheumatoid arthritis.

TABLE 2. Ethnic variability in methotrexate pharmacogenetic associations and clinical implications

Gene	Key Polymorphism(s)	Role in MTX Pharmacological Pathway	Caucasian Ancestry	Asian Ancestry	Middle Eastern ancestry	Direction of Association
SLC19A1 (RFC1)	rs1051266 (G80A)	Cellular uptake of MTX	Positive response[15,21] and, protection effects against MTX-related toxicity[25]	Potential efficacy,[27,28] Chinese studies report associations with efficacy and toxicity[22]	Favorable response[23]	Ethnicity-dependent, inconsistent
MTHFR	C677T, A1298C; rs1742151 1, rs1476413, rs4846051	Folate metabolism regulation	Associations with MTX toxicity and disease activity reported, but inconsistent for efficacy	Chinese cohorts reported associations with disease activity and toxicity, but limited predictive value for MTX response	Limited evidence; may contribute to higher toxicity of MTX[36] in elevated hepatic enzyme	Variable; ethnicity-dependent, limited predictive value Variable; stronger for toxicity than efficacy
FPGS	rs10106, rs1544105, A1994G and others	Intracellular MTX polyglutamation	Associated with MTX response, treatment persistence, and toxicity in European (Spanish) cohorts	Japanese and South Indian Tamil studies demonstrate effects on MTX polyglutamate formation and adverse events; Malaysian data heterogeneous[15,28,32]	Very limited or no population-specific data reported	Population-specific; associated with both efficacy and toxicity
GGH	rrs11545078, rs3758149	MTX deglutamation	Heterogeneous findings; some studies report trends with MTX efficacy or toxicity[40,41]	Predominantly null associations reported across multiple Asian cohorts	No population-specific data	Inconsistent finding
ATIC	rs2372536 (C347G), rs4673993 (T675C)	Folate-dependent pathway; inhibition of de novo purine synthesis and adenosine-mediated anti-inflammatory effects	Several studies report positive associations with MTX efficacy and treatment respons	Malaysian cohort (n=647) showed significant associations with MTX efficacy; Chinese cohorts reported no significant association[15,20]	Very limited	Population-specific; inconsistent
ABC transporters (ABCB1 ABCC2, ABCG2)	rs1045642 (C3435T), rs2032582 (G2677T/A), rs1128503 rs717620 (–24C>T), rs2273697 (1249G>A)	MTX efflux	Exploratory evidence that may have an efficacy relation of MTX[42]	More consistently reported associations with MTX	Limited data; mostly exploratory with no consistent associations	Inconsistent / population-dependent

TABLE 3. Methodological Sources of Heterogeneity in Methotrexate Pharmacogenetic Studies and Implications for Future Research

Methodological Domain	Identified Limitation	Impact on Evidence Interpretation	Implication for Future Studies
Outcome definition	Heterogeneous endpoints (EULAR response, DAS28, discontinuation)	Poor comparability across studies	Use standardized disease activity measures (e.g., DAS28)
Population structure	Underrepresentation of Southeast Asian populations	Limited external validity	Conduct population-specific pharmacogenetic studies
MTX exposure	Variability in dose, route, and folate supplementation	Confounding genetic associations	Standardize MTX regimen or adjust analytically
Sample size	Small cohort sizes	Low statistical power	Prospective sample size estimation
Confounding control	Limited adjustment for steroids and csDMARDs	Risk of biased associations	Multivariable regression analysis
Genetic modeling	Inconsistent inheritance models	Divergent findings	Pre-specified genetic models with sensitivity analyses

DISCUSSION

This narrative review highlights substantial ethnic variability in reported methotrexate (MTX) pharmacogenetic associations among patients with rheumatoid arthritis. Although several genetic polymorphisms within the MTX pharmacological pathway demonstrate strong biological plausibility, their observed clinical relevance remains highly population-dependent, with inconsistent associations reported across different ethnic groups.[8,32,38,44] These discrepancies likely reflect differences in allele frequencies, haplotype structures, linkage disequilibrium patterns, and broader population-specific genetic architectures. In addition, methodological heterogeneity across studies, including variations in study design, MTX dosing regimens, folate supplementation, outcome definitions, and analytical approaches, further limits the comparability and reproducibility of existing findings.

In this regard, genetic risk, as reflected by polygenic risk scores, represents the cumulative burden of multiple susceptibility variants that predispose individuals to immune dysregulation and chronic inflammation. While genetic predisposition alone may be insufficient to initiate rheumatoid arthritis, its interaction with accelerated biological ageing appears to substantially amplify disease risk. This interaction highlights a synergistic relationship between inherited vulnerability and age-related physiological decline, providing a more integrative framework for understanding disease susceptibility and therapeutic heterogeneity.[45] Ethnic variability in MTX pharmacogenetic associations is likely influenced by differences in population-specific genetic architecture, including allele frequency distributions, haplotype structures, and linkage disequilibrium patterns. Polymorphisms in key MTX-related genes such as SLC19A1, MTHFR, ATIC, and members of the ATP-binding cassette (ABC) transporter family exhibit marked interethnic differences in allele prevalence.[46,47] These variations may alter the functional impact of genetic variants on MTX pharmacokinetics and pharmacodynamics, thereby modifying their clinical associations across

populations.[8,44] Among these, SLC19A1 (RFC1) has been the most consistently investigated, given its central role in MTX cellular uptake. While several studies in Caucasian populations have reported positive associations between rs1051266 and treatment response, findings from Asian populations have been less consistent, and evidence from Southeast Asian cohorts remains limited. These discrepancies may partly reflect ethnic differences in allele frequencies and linkage disequilibrium patterns, which influence the functional impact of genetic variants across populations. The heterogeneity observed across studies reflects not only differences in genetic architecture between ethnic groups but also methodological variability in study design, treatment exposure, and outcome assessment. Similarly, polymorphisms in MTHFR, a key regulator of folate metabolism, have shown more consistent associations with MTX-related toxicity than with treatment efficacy, particularly in East Asian populations. This pattern suggests that folate pathway variants may exert a greater influence on adverse drug reactions than on therapeutic response. However, inconsistent findings across ethnic groups underscore the complexity of MTX pharmacogenetics and caution against extrapolating results derived from one population to another without validation.

Genes involved in intracellular MTX metabolism, including FPGS and GGH, remain underexplored in clinical pharmacogenetic studies. Although these enzymes play a critical role in determining intracellular MTX polyglutamate levels, available evidence demonstrates inconsistent or null associations with clinical outcomes. The lack of large, well-powered studies limits the ability to clarify their contribution to ethnic variability in MTX response. These findings highlight a disconnect between strong mechanistic plausibility and limited clinical validation, a recurring challenge in pharmacogenomic research.

Polymorphisms in ATIC, which influence purine synthesis inhibition and adenosine-mediated anti-inflammatory effects, illustrate the importance of population-specific effects. While some Caucasian studies have reported positive associations with MTX efficacy, findings in East Asian populations have been mixed, and data from Southeast Asia remain scarce. This pattern suggests that ATIC-related associations may be context-dependent and influenced by population-specific genetic backgrounds.

Likewise, genetic variation in ABC transporters involved in MTX efflux has been examined primarily through exploratory analyses. Although limited evidence suggests potential associations with MTX toxicity or drug disposition in Caucasian and East Asian populations, the absence of comprehensive studies in Southeast Asian cohorts precludes definitive conclusions. These findings further emphasize the need for population-specific investigations before clinical implementation can be considered.

Beyond genetic factors, methodological heterogeneity represents a major contributor to inconsistent pharmacogenetic findings. Differences in MTX dosing strategies, folate supplementation, concomitant therapies, and outcome definitions complicate cross-study comparisons and may obscure true genetic effects. The use of heterogeneous clinical endpoints, such as EULAR response, DAS28 scores, or treatment discontinuation, further limits comparability across ethnic groups. Standardization of outcome measures and analytical approaches is therefore essential to advance the field.[19] The limited and fragmented evidence from Asian populations represents a critical gap in the current pharmacogenetic literature. Given the ethnic diversity within Southeast Asia itself, reliance on data derived from Caucasian or East Asian populations may lead to inaccurate assumptions regarding MTX response and toxicity in this region.

At present, available evidence does not support routine genotype-guided MTX therapy in Southeast Asian moreover Indonesia patients. Instead, careful clinical monitoring remains the cornerstone of MTX management until robust, population-specific data become available.

Future research on methotrexate pharmacogenetics in rheumatoid arthritis should increasingly focus on genetic determinants that occupy central, biologically non-redundant positions within the methotrexate pharmacological pathway.[15,22] Among the wide range of candidate genes evaluated to date, SLC19A1, FPGS, and ATIC remain particularly relevant due to their sequential and complementary roles in methotrexate transport, intracellular activation, and downstream anti-inflammatory signalling. SLC19A1 encodes the reduced folate carrier responsible for cellular methotrexate uptake, thereby influencing intracellular drug availability. FPGS regulates polyglutamation, a critical process determining methotrexate retention and sustained inhibition of folate-dependent enzymes, while ATIC functions downstream in the folate pathway and contributes to AICAR accumulation and adenosine-mediated anti-inflammatory effects, a mechanism widely recognized as central to methotrexate efficacy in rheumatoid arthritis.[21,32,43,44] Given their mechanistic positioning, genetic variation in these loci is biologically well placed to contribute to interindividual differences in treatment response.

Despite this strong biological plausibility, associations between polymorphisms in SLC19A1, FPGS, and ATIC and methotrexate efficacy have shown substantial variability across racial and ethnic populations. Studies conducted in Caucasian, European, Middle Eastern, and Asian cohorts have reported inconsistent findings with respect to both the direction and magnitude of genetic effects, reflecting differences in genetic architecture, allele frequency distribution, linkage disequilibrium patterns, clinical outcome definitions, and study design.[18,30,48] From a global health perspective, addressing underrepresented and genetically diverse populations is essential to ensure equitable development of precision medicine. Notably, the insufficient data from Southeast Asian populations limits extrapolation of findings and emphasizes the need for standardized outcome measures such as the Disease Activity Score-28 (DAS28). Population-specific investigations are essential to clarify the clinical relevance of MTX pharmacogenetics in regional practice.

Indonesia represents a particularly informative setting for future pharmacogenetic research due to its pronounced population heterogeneity arising from complex admixture and regional substructure across the archipelago. These characteristics have important implications for allele frequency spectra and linkage disequilibrium structure, both of which may influence the detection, reproducibility, and clinical interpretation of pharmacogenetic associations.This concern is clinically salient given that methotrexate remains the recommended first-line conventional synthetic disease-modifying antirheumatic drug in rheumatoid arthritis management, including in low- and middle-income settings, while pharmacogenetic evidence from Indonesian populations remains limited.[5,49] Targeted pharmacogenetic studies in Indonesian cohorts focusing on SLC19A1, FPGS, and ATIC variants would therefore contribute valuable evidence to clarify their clinical relevance, support context-appropriate optimization of methotrexate therapy, and strengthen the global pharmacogenetic knowledge base in rheumatoid arthritis.

Beyond gene selection, the choice of population is pivotal for interpreting and generalizing pharmacogenetic findings. Indonesia is a particularly informative priority setting because

its population structure is highly heterogeneous, shaped by complex admixture and regional substructure across the archipelago; such features can materially alter allele frequencies, linkage disequilibrium patterns, and observed effect sizesprecisely the conditions under which extrapolation from more genetically homogeneous cohorts becomes least reliable.This methodological concern is clinically consequential because methotrexate remains the globally recommended first-line csDMARD backbone in rheumatoid arthritis management, yet pharmacogenetic evidence from genetically diverse and historically underrepresented populations remains limited.[5,49] Therefore, well-designed Indonesian cohorts ideally multi-center and explicitly accounting for sub-ethnic structure would not only clarify the translational relevance of SLC19A1, FPGS, and ATIC variants for methotrexate efficacy, but also contribute to reducing inequities in the evidence base that currently constrains equitable implementation of precision medicine worldwide.[18,19]

CONCLUSION

Ethnic variability appears to play an important role in methotrexate pharmacogenetic associations among patients with rheumatoid arthritis and may partly explain the inconsistent findings reported across different populations. Variations in allele frequencies, population structure, and methotrexate-related pharmacological pathways can influence treatment response, toxicity, and overall clinical outcomes. Current evidence suggests that polymorphisms involved in methotrexate transport, intracellular metabolism, folate-dependent pathways, and drug efflux mechanisms may exhibit population-specific effects, although the findings remain heterogeneous across studies due to differences in study design, outcome definitions, and analytical approaches. In particular, pharmacogenetic data from Southeast Asian populations are still limited, highlighting the need for further population-specific investigations. Future studies using standardized clinical outcome measures and more diverse ethnic representation are needed to improve the consistency, reproducibility, and clinical applicability of methotrexate pharmacogenetics in supporting precision medicine approaches for rheumatoid arthritis management.

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